Remarks

The Interview

Applicants greatly appreciate the opportunity to interview this case on October 21, 1997, with the Examiner, Mike Wityshyn and Margaret Parr. The interview was very helpful in providing Dr. Edelman with an opportunity to explain restenosis and why the prior art efforts to utilize a pharmacological therapy have not been effective in preventing smooth muscle cell proliferation and why one cannot simply replace the endothelial cell monolayer on the arterial surface and avoid smooth muscle cell proliferation. The independent claims have been amended to insert the phrase "without migration of the endothelial cells to the arterial lining", as agreed at the interview to more explicitly exclude vascular tissue grafts from the claimed method and composition. Support for this amendment is found, for example, at page 20, lines 4-5. A copy of all the pending claims as they are believed to have been amended is attached to this Amendment as an appendix.

Rejections under 35 U.S.C. §112, second paragraph

Claims 1-10 and 18 were rejected under 35 U.S.C. §112, second paragraph, as indefinite or lacking support. These rejections are respectfully traversed if applied to the amended claims.

The phrase "without needing restoration of the endothelial cell lining of the blood vessel" has been deleted.

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AMENDMENT

As agreed at the interview, the alternative language has been eliminated from the Markush claims.

The phrase "compounds regulating the renin-angiotensin axis" has been deleted to facilitate prosecution.

Claim 14 has been amended to delete the term "genetically engineered cells" and to add the phrase in a new dependent claim 20.

As discussed at the interview, "coronary artery bypass surgery" refers to surgery involving the arteries in the vicinity of the heart; "peripheral bypass surgery" refers to surgery anywhere else. "Organ transplantation" was discussed as being an art recognized term.

Rejections under 35 U.S.C. §103

Claims 1-18 were rejected under 35 U.S.C. §103 as obvious over U.S. Patent No. 5,540,928 to Edelman, U.S. Patent No. 5,455,039 to Edelman, or U.S. Patent No. 5,527,532 to Edelman in view of the prior art discussed at the bottom of page 2 to the top of page 3 of the specification, in combination with U.S. Patent No. 4,787,900 to Yannas or U.S. Patent No. 5,567,612 to Vacanti *et al.*, alone or in further combination with U.S. Patent No. 4,418,691 to Yannas *et al.*, or U.S. Patent No. 5,299,665 to Barrera *et al.* These rejections are respectfully traversed if applied to the amended claims.

As discussed at the interview, the inventors have discovered that neither reconstruction of the monolayer of endothelial cells lining the artery, either by means of

culturing dissociated cells on a matrix to form new blood vessels (using the tissue engineering described by either Yannas or Vacanti) or vascular grafts, nor localized drug delivery (Edelman), can reduce smooth muscle cell proliferation at a site of vascular injury, to the extent that one can obtain by administering a very large number of endothelial cells in a polymeric matrix at the site of the injury. Figure 3 actually compares the effectiveness of heparin (described by Edelman) ("HEP") with the effectiveness of the endothelial cells in a polymeric matrix applied at the site of injury ("EC"). The results obtained with the endothelial cells are significantly, and unexpectedly, better. Data from pigs which was presented at the interview further supported the significantly and unexpectedly better results obtained with the endothelial cell-polymeric implant.

The prior art discussed at pages 2-3 of the specification does not disclose that restoration of the endothelial cell lining of the arteries prevents or inhibits smooth muscle cell proliferation. Instead, it reports that the **normal** role of the endothelial monolayer is to inhibit abnormal smooth muscle cell proliferation. Applicants' claims are directed to treatment of conditions where the normal endothelial monolayer has been disrupted. Schwartz *et al.* and Fisherman *et al.*, cited in the specification at the bottom of page 2, report that excessive proliferation ceases in rats after about one year following injury. Such cessation is too late to prevent occlusion or obstruction in humans, since most patients develop restenosis (occlusion or obstruction of the blood vessel wall following injury) within three to six months of the injury, and since the mechanisms responsible (thrombus deposition, inflammation,

proliferation, and remodeling) are most pronounced within the first month following injury. Additionally, vascular grafts or reconstruction do not prevent smooth muscle cell proliferation in blood vessels following injury. For example, Conte *et al.*, "Endothelial cell seeding fails to attenuate intimal thickening in balloon-injured rabbit arteries", J. Vascular Surgery 21(3):413-21 (1995), a copy of which is attached, expressly states that endothelial seeding fails to inhibit intimal hyperplasia (see also Westerband *et al.*, "Immunocytochemical determination of cell type and proliferation rate in human vein graft stenoses", J. Vascular Surgery 25(1):64-73 (1997), a copy of which is attached). Dr. Edelman explained that the failure of conventional methods to restore the endothelial lining is because endothelial cells do not adhere well or remain in place when subjected to shear, turbulent flow, and alterations in the injured vessel wall. Moreover, it is not possible to restore the normal blood vessel wall configuration within the critical time frame.

None of the prior art disclosed or even suggested that the placement on the arterial lining was not critical. In fact, the prior art (or dogma) was that the control elicited by endothelial cells relied on restoration of the endothelial monolayer at the lumenal interface, not that one could apply endothelial cells elsewhere and inhibit abnormal cellular proliferation (see, for example, Conte *et al.*, Circulation, 89:2161-69 (1994), a copy of which is attached). Applicants' demonstration of control without restoration of the monolayer is contrary to expectation.

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Allowance of claims 1-18, as amended, and new claim 20, is earnestly solicited.

Respectfully submitted,

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CERTIFICATE OF FACSIMILE TRANSMISSION

I hereby certify that this Amendment, along with any papers indicated as being attached, is being facsimile transmitted to the U. S. Patent and Trademark Office on the date shown below.

Date: October 28, 1997

Terry Welch